Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes

This activity was developed by the American Pharmacists Association and the Agency for Healthcare Research and Quality.

Speakers

Moderator

Barbara A. Bartman, M.D., M.P.H.

Medical Officer

Agency for Healthcare Research and Quality

Effective Health Care

Speaker One

Scott Smith, R.Ph., M.S.P.H., Ph.D.

Director of Pharmaceutical Outcomes Research

Agency for Healthcare Research and Quality

Effective Health Care

Speaker Two

Rehan Qayyum, M.D.

Assistant Professor of Medicine

The Johns Hopkins University School of Medicine

Investigator

Evidence-based Practice Center

The Johns Hopkins University

Baltimore, MD

Speaker Three

Carmen Kelly, Pharm.D, R.Ph.

Pharmacist Officer

Agency for Healthcare Research and Quality

Effective Health Care

Accreditation

APhA is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. The ACPE Universal Activity Number assigned to the activity by the accredited provider is: **202-999-09-111-L01-P**. This activity is approved for 1 contact hour of continuing pharmacy education credit (0.1 CEU).

To obtain continuing pharmacy education credit for this activity, participants must participate in the entire activity, and complete the online activity evaluation form located on www.pharmacist.com by March 13, 2009. A Statement of Credit will be automatically generated upon achieving these requirements. There is no fee to participate in this activity.

ACPE Activity Type: Knowledge-Based
Initial Release Date: February 26, 2009

Disclosures

Barbara A. Bartman, M.D., M.P.H., Scott Smith, R.Ph., M.S.P.H., Ph.D., and Carmen Kelly, Pharm.D, R.Ph. have no financial interests or relationships to disclose.

Rehan Qayyum, M.D. received grant support from the Agency for Healthcare Research and Quality (AHRQ) through contract #290-02-0018.

AHRQ's Office of Communications and Knowledge Transfer staff, The Lewin Group project staff, and APhA's editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Learning Objectives

- To discuss the effectiveness of premixed insulin analogues in achieving optimal glycemic control, as compared to insulin regimens
- To compare the differences in premixed insulin analogues from other commonly used insulin preparations with regard to safety, adverse effects, or adherence
- To evaluate the effectiveness and safety of the new premixed insulin analogue regimens in individuals on oral anti-diabetic agents and individuals with different blood glucose patterns or types of control
- To discuss practical and effective therapy options for patients with diabetes

The Effective Health Care Program

Scott Smith, R.Ph., M.S.P.H., Ph.D.

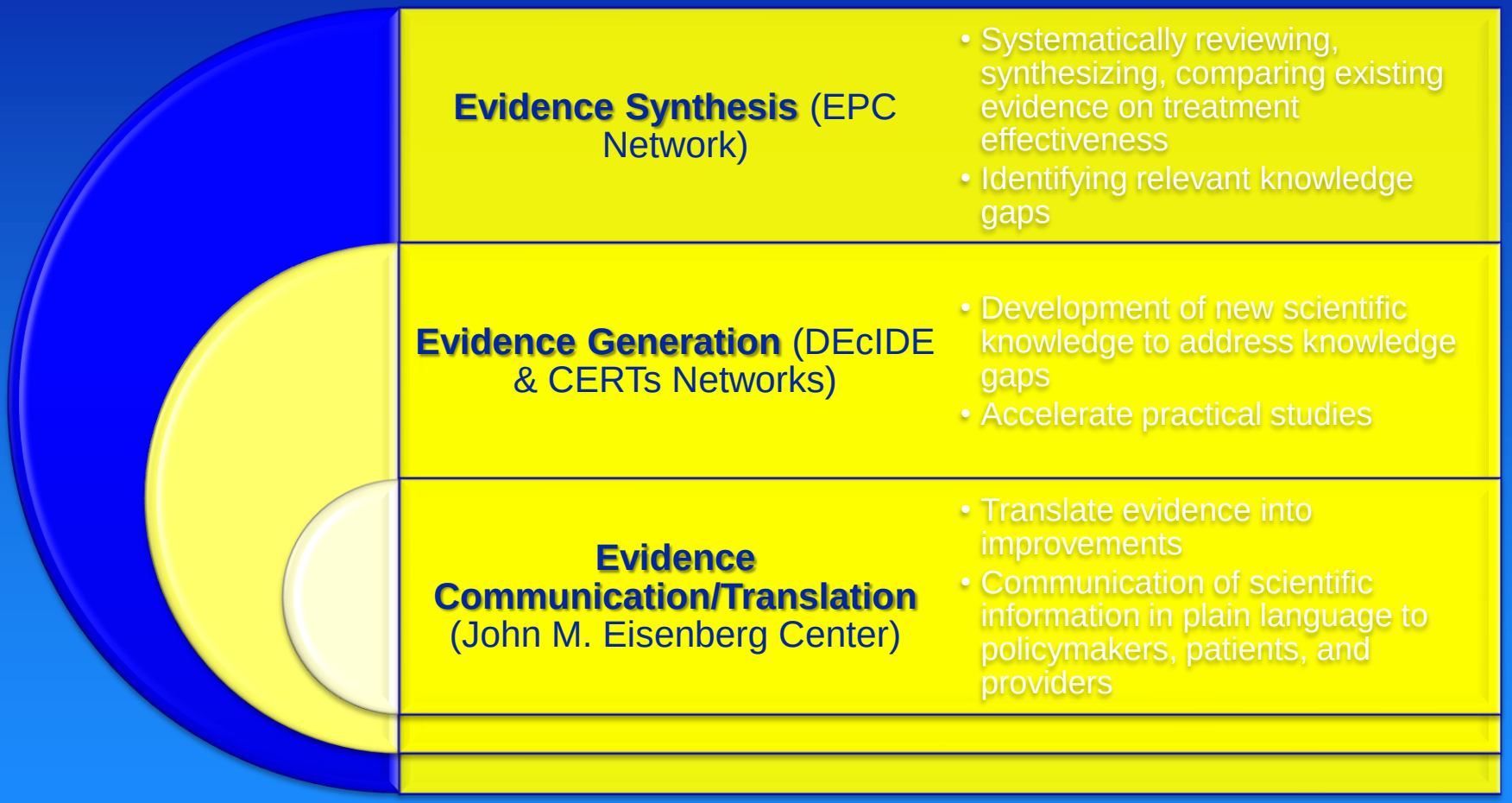
Agency for Healthcare Research and Quality

Effective Health Care

Effective Health Care Program 2003 – Present

- Authorized in 2003 by Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act
- Conducts objective comparisons of the effectiveness of different health care interventions
- Goal: To support informed health care decisions by patients, clinicians, and policymakers and improve the quality, effectiveness, and efficiency of health care to support evidence-based practice

Effective Health Care Program



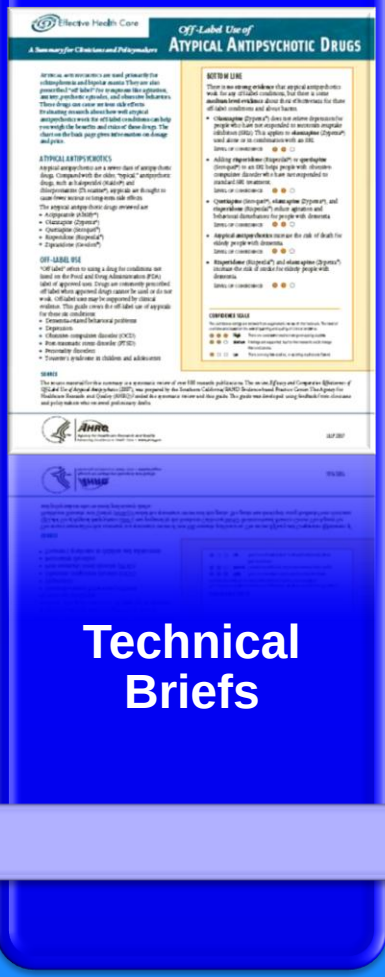
Approaches to Research

- **Synthesizes** existing scientific evidence
- **Generates** new scientific evidence to address gaps
- **Translates** research into plain-language guides

Available Products

Research Reviews

New Research Reports



Technical Briefs

Summary Guides

How Products Are Used

- ✓ Inform clinical guideline development
- ✓ Identify future research priorities
- ✓ Inform policy, including coverage decisions
- ✓ Inform clinician and patient decisions

How to Obtain Reports

- www.effectivehealthcare.ahrq.gov
  - Full reports and Summary Guides
  - Audio files
  - Spanish translations
- AHRQ Publications: (800) 358-9295
  - Requests for free printed Summary Guides

How to Stay Informed

- ✓ EHC Web site
- ✓ E-mail notices

Contacts

AHRQ Effective Health Care E-mail:

effectivehealthcare@ahrq.gov

Speaker Contact:

Scott R. Smith, R.Ph., Ph.D.

Scott.Smith@ahrq.hhs.gov

AHRQ

Agency for Healthcare Research and Quality

Advancing Excellence in Health Care

www.ahrq.gov

Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes

Rehan Qayyum, M.D.

Johns Hopkins School of Medicine

Evidence-based Practice Center

Scope of Problem

- Diabetes – 7th leading cause of death
  - as listed on death certificates; likely to be under-reported
- Patients with diabetes have twice the risk for death than those without diabetes
- Annual direct medical costs = $116 billion
  - 2.3 times higher expenditures in patients with diabetes than would be in its absence

National diabetes fact sheet 2007. CDC, Atlanta, GA. 2008

Glucose Control in Type 2 Diabetes

- Optimal control of hyperglycemia prevents or delays diabetic complications
- 10% decrease in mortality and 25% decrease in microvascular complications with intensive vs. conventional glucose control in patients with type 2 diabetes (UKPDS)
- Suboptimal glucose control with oral hypoglycemic agents → insulin
- 22% of type 2 diabetes patients take insulin

UKPDS. Lancet. 1998;352:837-853.
National diabetes fact sheet 2007. CDC, Atlanta, GA. 2008

Key Questions - 1

- In adults with type 2 diabetes, what is the **effectiveness** of premixed insulin analogues in achieving optimal glycemic control as compared to insulin regimens including the following preparations?
  - Premixed human insulin preparations
  - Long-acting insulin analogues administered alone
  - Intermediate-acting human insulin administered alone
  - Short-acting (regular) human insulin administered prandially
  - Rapid-acting insulin analogues administered separately (prandially) with a long-acting insulin analogue

Key Questions - 2

- For adults with type 2 diabetes, do premixed insulin analogues differ from other commonly used insulin preparations with regard to **safety, adverse effects, or adherence**?
  - The adverse effects of interest include, but are not limited to, hypoglycemia (nocturnal and daytime), weight gain, and interactions with other medications.

Key Questions - 3

- Does the effectiveness or safety of the new premixed insulin analogue regimens vary across the following **subpopulations** of patients with type 2 diabetes?
  - The elderly (≥ 65 yrs), very elderly (≥ 85 yrs)
  - Other demographic groups (ethnic or racial groups)
  - Individuals with comorbid medical conditions
  - Individuals with limited life expectancy
  - Individuals with disabilities

Key Questions - 4

- What are the **effectiveness and safety** of the new premixed insulin analogue regimens in individuals **on oral anti-diabetic agents** and individuals with **different blood glucose patterns** (such as fasting hyperglycemia or postprandial hyperglycemia) or **types of control** (such as tight control, usual control, good fasting or postprandial control)?

Methods – Search Strategy

- Electronic Databases (February 2008)
  - MEDLINE, EMBASE, CENTRAL (The Cochrane Central Register of Controlled Trials), CINAHL
- Hand Search
  - 13 journals specific to the field
  - References of included articles
- Web Sites
  - FDA, EMEA, clinicalstudyresults.org, clinicaltrials.gov
- Scientific information packets submitted by Eli Lilly, Sanofi-Aventis, Novo Nordisk

Methods – Study Section

- Included:
  - Controlled clinical trials, crossover trials, and observational studies published in English-language peer-reviewed journals
- Excluded:
  - Editorials, comments, letters, and abstracts
- Two reviewers independently selected studies

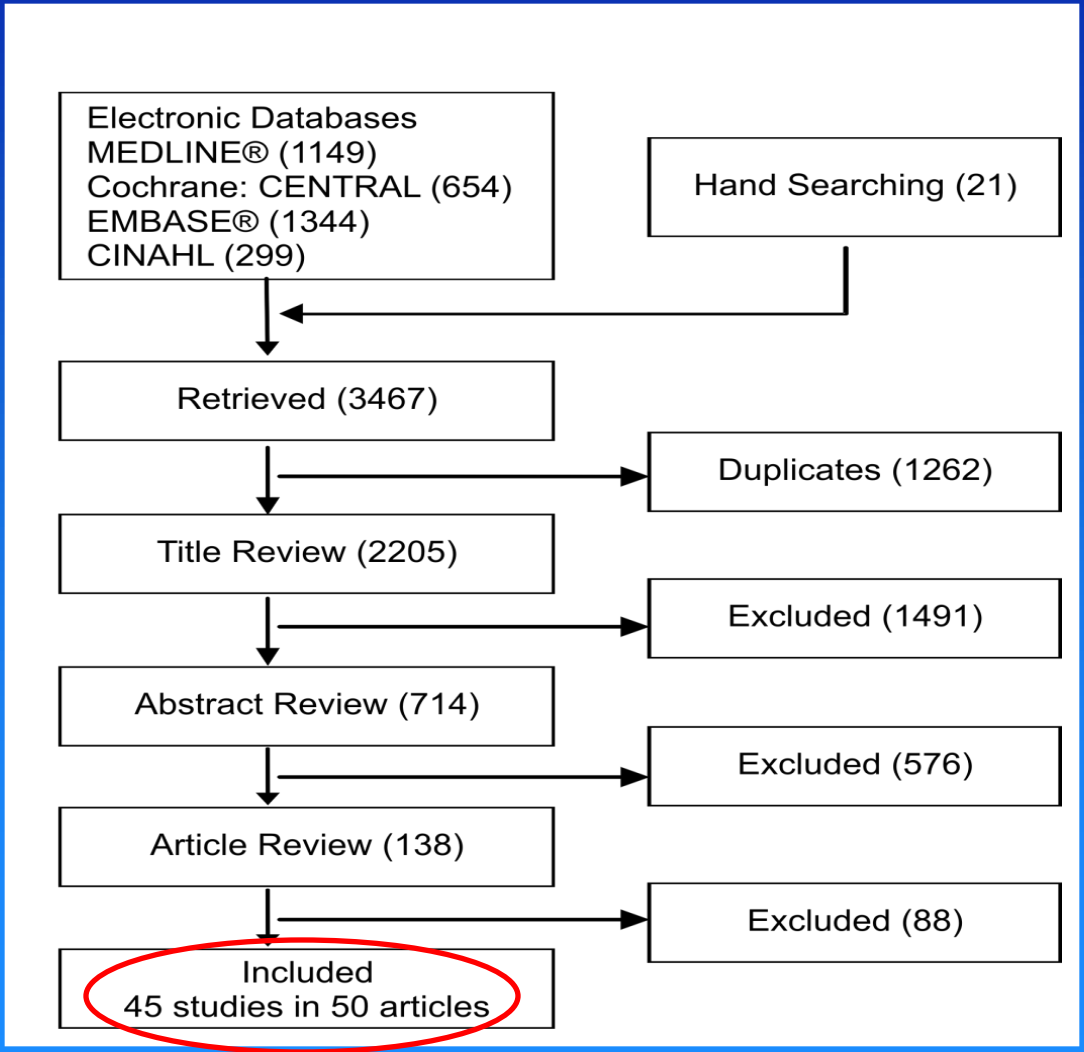
Methods – Data Synthesis

- Intermediate outcomes (fasting and postprandial glucose, A1c)
  - Random effects model
- Adverse effects (hypoglycemia, weight change)
  - Random effects model
- Clinical outcomes (rare-event data)
  - Fixed effects model (Mantel-Haenszel)
  - Sensitivity analysis with Peto's method and Bayesian random-effects model

Grading of Stretch of Evidence

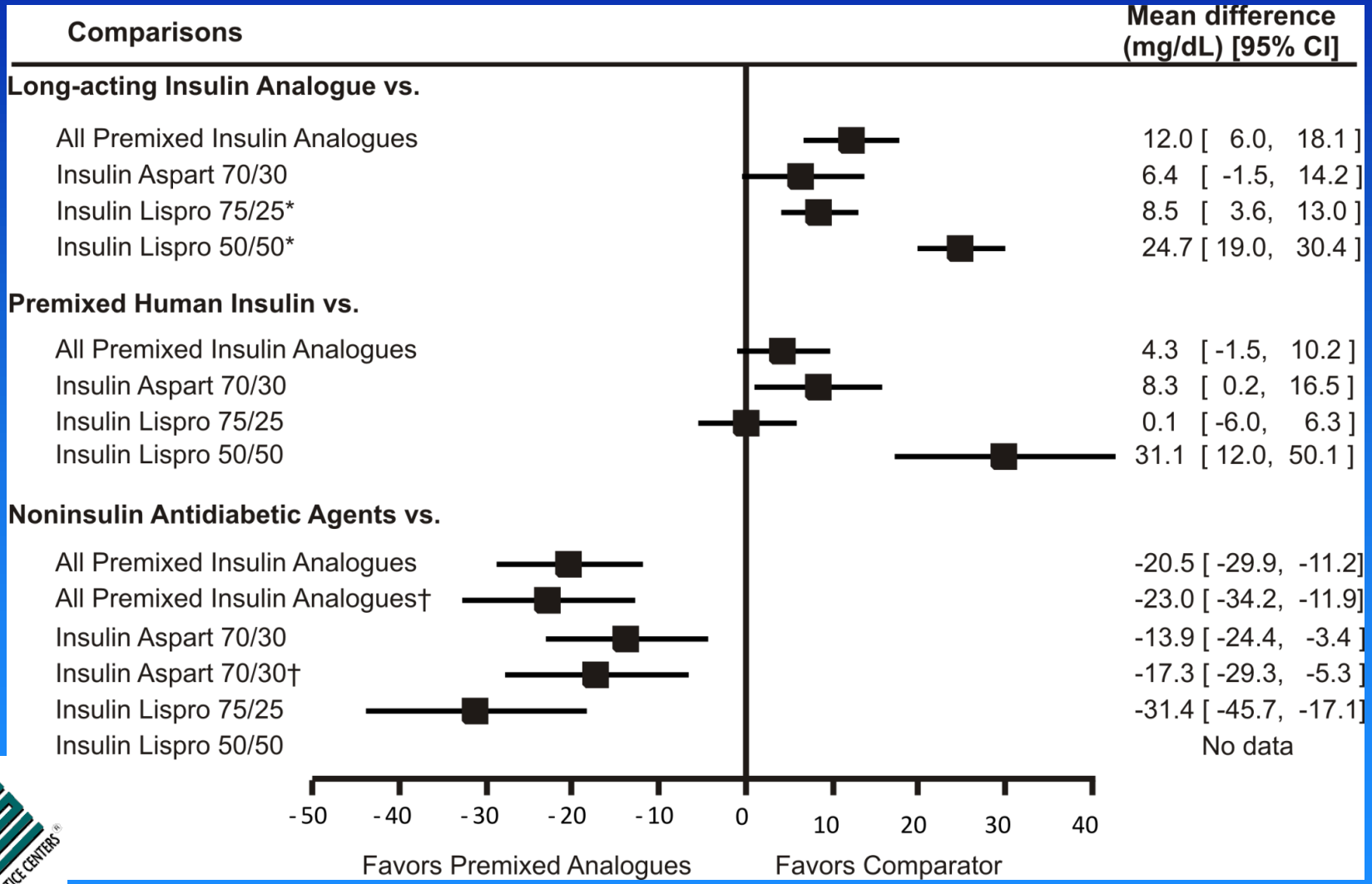
- Grading scheme of the GRADE Working Group
- Focus was on
  - Study design
  - Number of studies
  - Quality of studies
  - Consistency of evidence
- Graded as high, moderate, low, or no evidence

Results



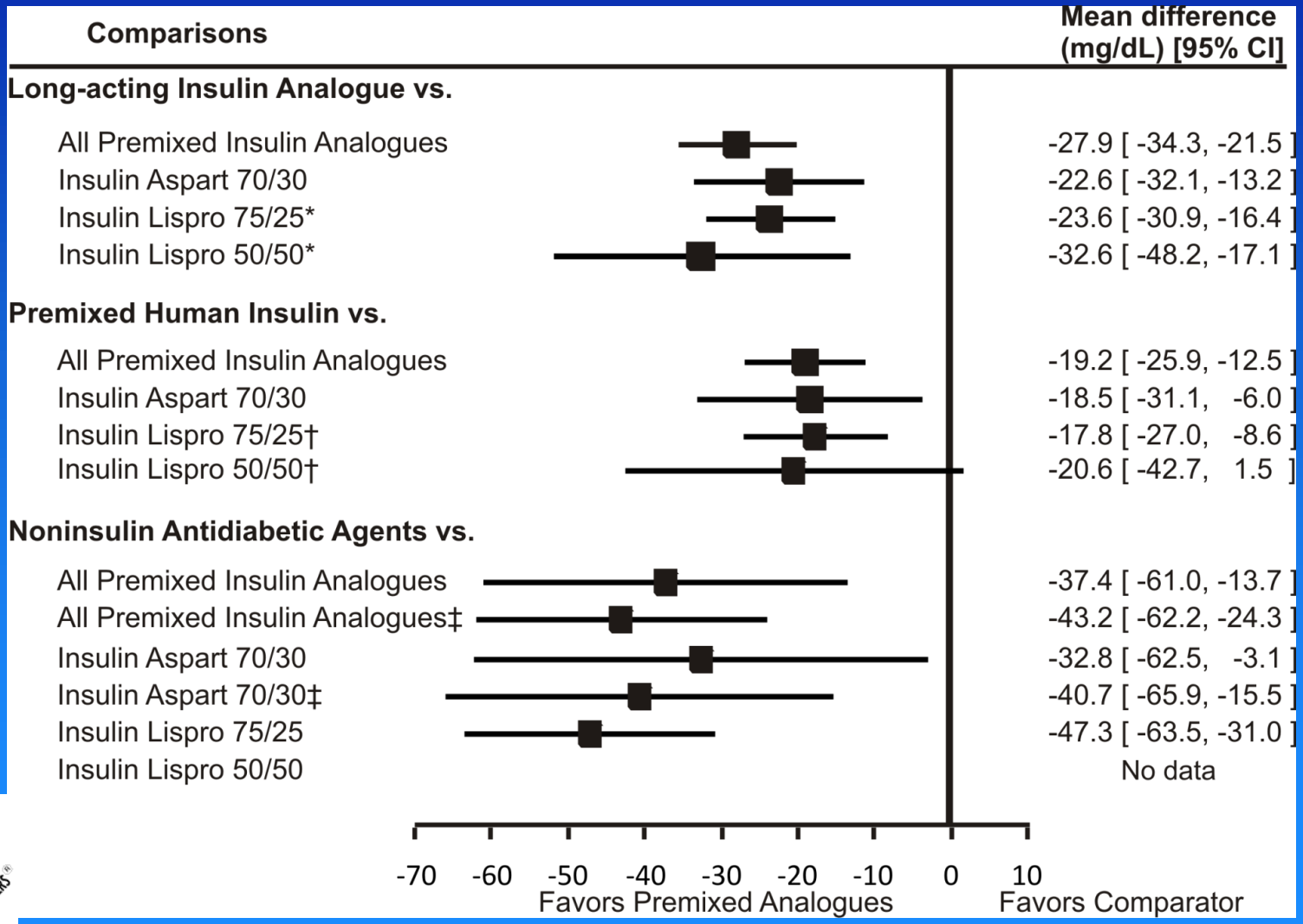
Qayyum et al. Ann Intern Med. 2008; 149:549-559.

Results – Fasting Glucose



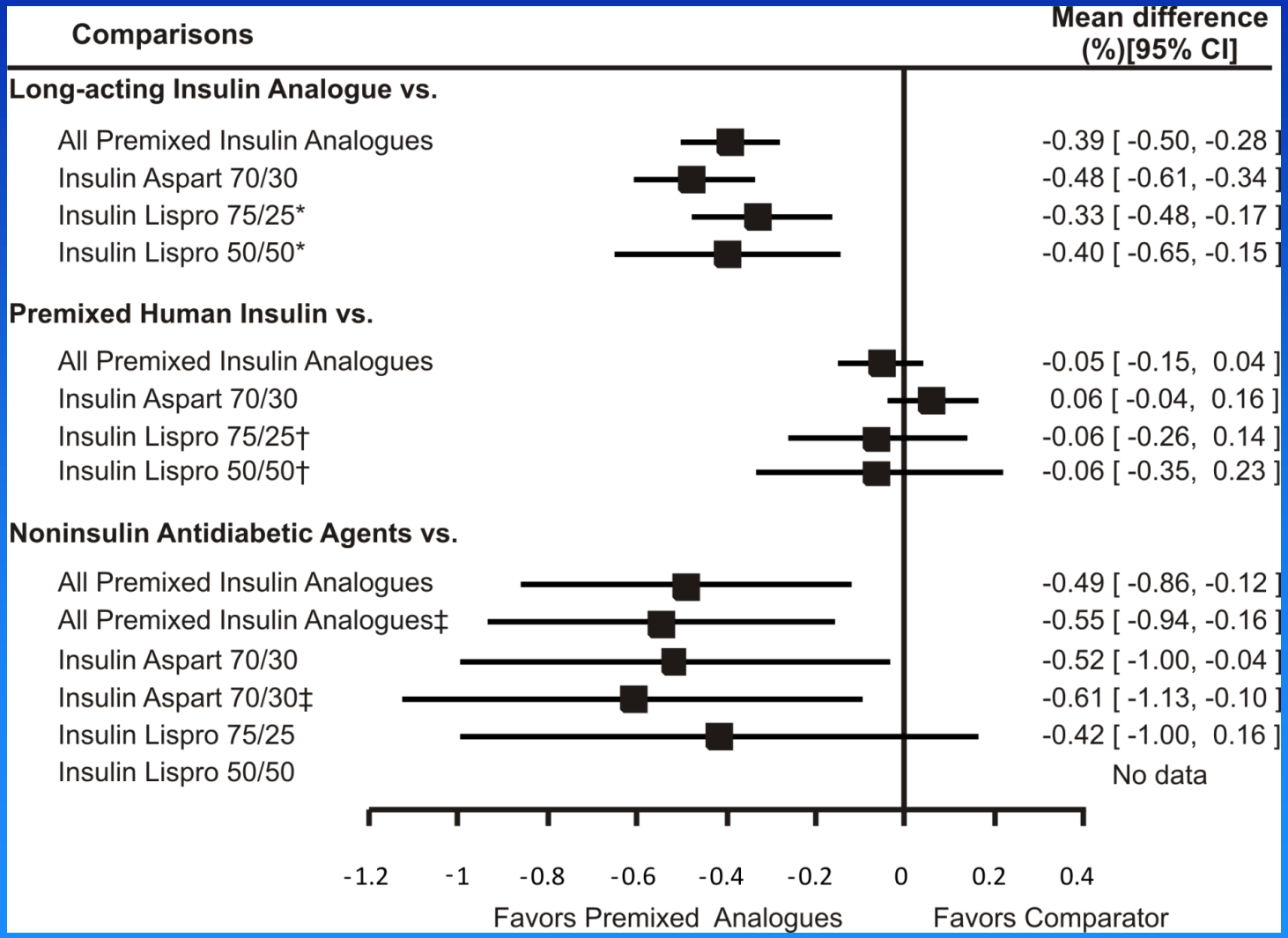
Qayyum et al. Ann Intern Med. 2008; 149:549-559.

Results – Postprandial Glucose



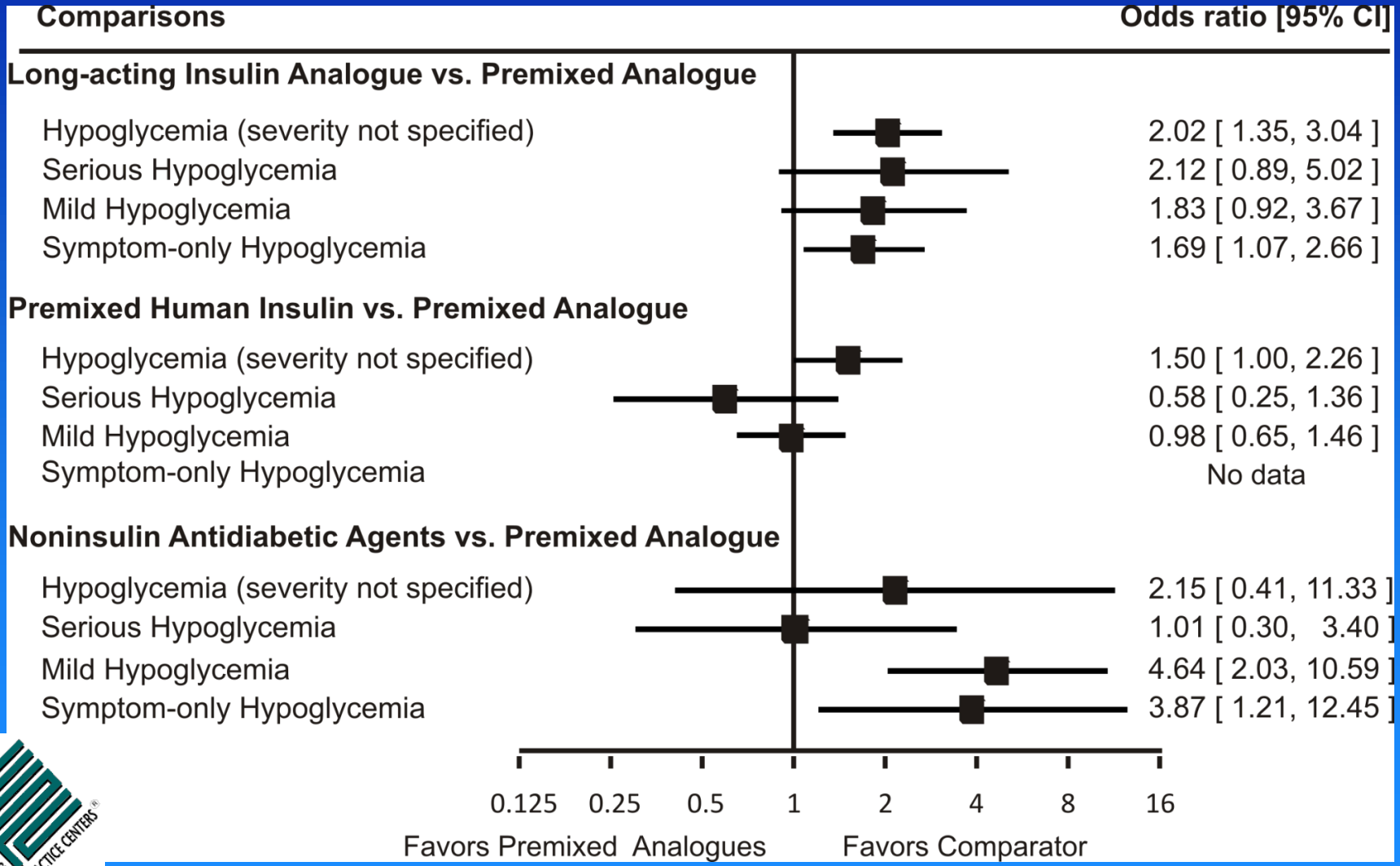
Qayyum et al. Ann Intern Med. 2008; 149:549-559.

Results – Hemoglobin A1C



Qayyum et al. Ann Intern Med. 2008; 149:549-559.

Results - Hypoglycemia



Qayyum et al. Ann Intern Med. 2008; 149:549-559.

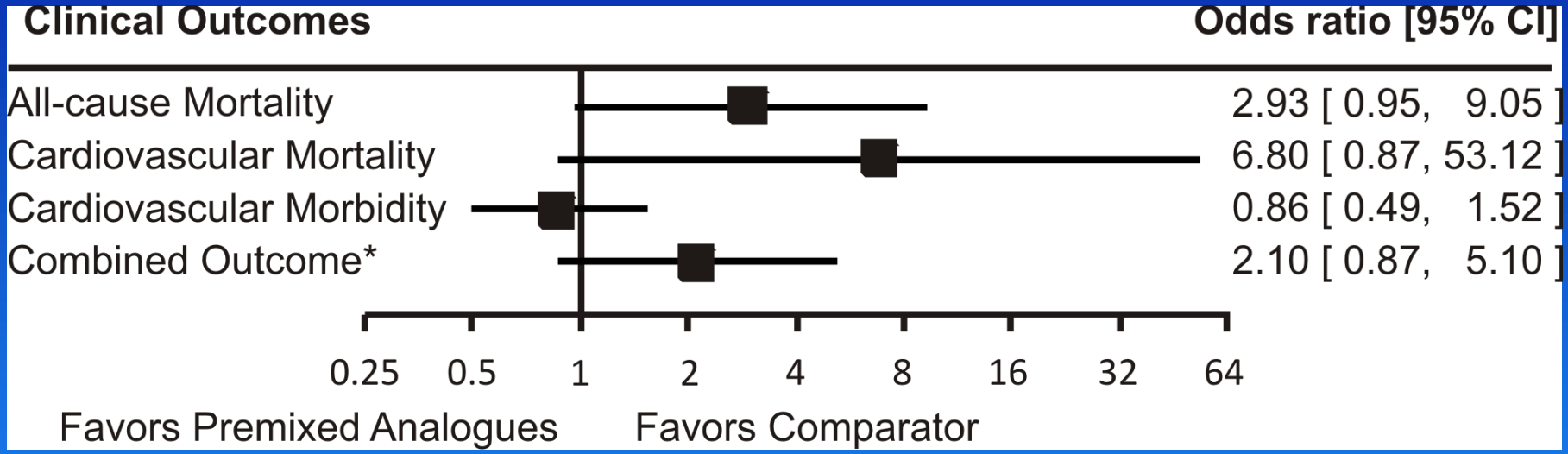
Results – Weight Change

		Mean (kg)	95%CI
Long-acting analogues vs.	All premixed analogues	-1.97	-1.22 to -2.73
	Insulin Aspart 70/30	-2.5	-1.6 to -3.4
	Insulin Lispro 75/25	**No data**	
	Insulin Lispro 50/50	-1.58	-0.99 to -2.18
Non-insulin antidiabetic agents vs.	All premixed analogues	-2.35	-0.84 to -3.86
	Insulin Aspart 70/30	-2.82	-0.61 to -5.02
	Insulin Lispro 75/25	-1.88	-1.35 to -2.41
	Insulin Lispro 50/50	**No data**	
Premixed human insulin vs.	All premixed analogues	**Not enough data**	

Results – Other Comparisons

No or scant data for other comparisons

Results – Clinical Outcomes



Qayyum et al. Ann Intern Med. 2008; 149:549-559.

Results – Quality of Life

- 6 studies evaluated this outcome
- In 4 studies using validated measurement tools, only one of six quality of life outcomes (psychological distress) showed a statistically significant difference, in favor of premixed insulin analogues over other anti-diabetic agents

Results – In Combinations with Oral Agents

- Fasting glucose, postprandial glucose, and hypoglycemia
  - 3 studies; no significant difference
- Hemoglobin A1c
  - 3 studies; combination better than premixed analogues alone
- Weight change and clinical outcomes
  - 2 studies; no significant difference

Results

- No evidence for:
  - Adherence to treatment regimen
  - Effectiveness and safety in subpopulations of interest
  - Different intensity of glucose control
  - Targeting fasting versus postprandial glucose control

Summary

		Long acting	Premixed	Noninsulin anti-diabetic
FBG	IA70/30	↔	↑	↓
	IL 75/25	↑	↔	↓
	IL 50/50	↑	↔	
PPBG	IA70/30	↓	↓	↓
	IL 75/25	↓	↓	↓
	IL 50/50	↓	↓	
HbA1c	IA70/30	↓	↔	↓
	IL 75/25	↓	↔	↔
	IL 50/50	↓	↓	
Hypoglycemia	IA70/30	↑	↔	↑
	IL 75/25	↑*	↔	↔
	IL 50/50	↑	↔	
Weight Change	IA70/30	↑	↔	↑
	IL 75/25		↔	↑
	IL 50/50	↑*	↔	

* Overall evidence is not of sufficient strength

Qayyum et al. Comparative Effectiveness Review No. 14. AHRQ, Rockville MD. 2008

Summary (cont'd.)

- Premixed analogues vs. long-acting analogues
  - Premixed better in lowering A1c and postprandial glucose
  - Less effective in lowering fasting glucose
- Premixed analogues vs. premixed human insulin
  - Better in lowering postprandial glucose
  - Similar in lowering A1c and fasting glucose
- Risk of hypoglycemia
  - Premixed analogue similar to premixed human insulin
  - Long-acting insulin analogues better than premixed analogue

Gaps in Evidence

- Scant data on clinical outcomes
- No effectiveness data
- Insufficient data on several comparisons of interest – e.g., basal-bolus regimen
- Short duration of followup
  - Scant data on continued clinical efficacy
  - No data on long-term harm
- Scant data on quality of life or adherence

Conclusion – Individualized Therapy

- **Problem – uncontrolled A1C**
  - Premixed analogues = Premixed human insulin
  - Premixed analogues > Long-acting, oral anti-diabetic
- **Problem - fasting hyperglycemia**
  - Premixed human insulin ≥ Premixed analogues
  - Long-acting > Premixed analogues
- **Problem – postprandial hyperglycemia**
  - Premixed analogues > Premixed human insulin, long-acting
- **Problem – hypoglycemia**
  - Premixed human insulin = Premixed analogues
  - Long-acting > Premixed analogues

Premixed Insulin Analogue Team

- Rehan Qayyum, M.D.
- Shari Bolen, M.D., M.P.H.
- Nisa Maruthur, M.D.
- Leonard Feldman, M.D.
- Lisa M. Wilson, Sc.M.
- Spyridon S. Marinopoulos, M.D., M.B.A.
- Padmini Ranasinghe, M.D., M.P.H.
- Muhammad Amer, M.D.
- Eric B. Bass, M.D., M.P.H.

Utility and Value of the Systematic Review: The Unique Position of Pharmacists

Carmen Kelly, Pharm.D., R.Ph.

Agency for Healthcare Research and Quality

Effective Health Care

Implications for Practice

- Ensuring optimal adherence
- Help patients make informed choices
- Cost considerations
- Safety issues

Implications for Research

- Comparative effectiveness research will further knowledge about which therapies work best for which individuals
- More research needed to “fill the gaps” identified in the report

Implications for Education

- Capacity to answer patient questions regarding insulin analogues
- Capacity to assist physicians and other health care providers in choosing the right insulin therapy, especially insulin analogues

Questions and Answers

To submit any followup questions, please e-mail us at:
AHRQScience2Practice@ahrq.hhs.gov

Obtaining CE Credit

To obtain continuing pharmacy education credit for this activity, participants must participate in the entire activity, complete the online activity evaluation form located on www.pharmacist.com by March 13, 2009, and enter the verification code **DCI226**.

A Statement of Credit will be automatically generated upon achieving these requirements.


DEPARTMENT OF HEALTH & HUMAN SERVICES • USA
AHRQ
Advancing
Excellence in
Health Care

THANK YOU